## REMARKS

Claims 1-4, 12, 18 and 21-24 were under consideration. Claims 5-11, 13-17, and 19-20 are reinstated and are also under consideration as per Examiner Zeman's instructions. Applicant had not cancelled these claims in his response of January 2, 2001 and now that the generic claim has been reviewed has reinstated them with Examiner's permission. Claim 12 is cancelled. Claim 18 is amended to correct deficiencies pointed out in the Action, under 35 U.S.C. §112. Applicant's attorney apologizes for any inconvenience because of these informalities. Claims 1-11 and 13-24 are amended. New claim 25 is added. Applicant's attorney is very grateful to Examiner Zeman for her assistance in clarifying the complexities in the unusual nature of the restriction requirement in this case.

The Action rejects claims 1-4 and 21-24 as being anticipated under 35 U.S.C. 102(e) by: 1) Armstrong et al. (U.S. Patent No. 6,099,469) and by 2) Carlson et al. (U.S. Patent No. 6,140,065) claims 1-4, 21-24, 12 and 18 under 35 U.S.C. 102(b) and by 3) Sreevatsan et al. (Journal of Clinical Biol. 1998, 36: 1895-1901). In response, applicant disagrees with these rejections based on the three cited references, for the reasons that follow:

Armstrong et al. U.S. Patent No. 6,099,469

The Action states that Armstrong et al. discloses a disease specific algorithm for use in a computer assisted method, which analyzes what clinical tests should be performed for acute myocardial infarction. A first test is performed on a sample, then, based upon the result of that test in comparison with preset guidelines, a

second test is run. The process is repeated until an endpoint ---the diagnosis of a condition --- is reached (col. 4-11). Figures 1B-1F set forth in the decision tree of clinical tests and diagnoses, and Figure 2 plus the discussion from col. 11, line 30 to col. 14, line 25, set forth the apparatus.

In response, Applicant concurs that Armstrong et al. describes a computer assisted method comprising a sequential process of testing biomarkers for myocardial infarction by a reflex algorithm, for use in the early diagnosis of acute myocardial infarction. However, Armstrong et al.'s reflex algorithm and its application in the diagnosis of myocardial infarction can be distinguished from the present invention. In fact, the present invention would be entirely non-enabling if applied in the diagnosis of myocardial infarction for the following reasons:

A. Armstrong et al.'s reflex algorithm is used to monitor a number of biochemical markers, which change in a time-sensitive manner during a myocardial infarction episode, for example creatinine kinase, myoglobin and troponin. These time dependent changes in the specific biomarkers are monitored by a technician in order to determine the stage at which the myocardial infarction is being monitored. And, sometimes, this requires that the same biomarker test be run repeatedly every four hours in order to follow the progression of the myocardial infarct. In other words, <u>it is the technician who decides as to whether to repeat any testing</u>. The reflex algorithm merely indicates how a measurement for a biomarker compares with a predetermined level.

In contrast, in the present invention, the algorithmic clinical testing allows a technician to load a sample and rely on a specific algorithm to execute the necessary tests in a sequential manner, to obtain an accurate diagnosis. The system is not time sensitive and as mentioned above, would be unsuitable to diagnose early phase of myocardial infarction because, once a test has shown to be negative, it is not repeated at intervals to see if it will turn to positive. The objective in the present invention is to provide a cost-effective system that can be used in the diagnosis of many diseases in which the markers being measured have stable values. The system is capable of carrying out intelligent programming to effectuate diagnosis and does not need the technician to make the decisions as is the case in Armstrong et al.

B. Armstrong et al. describes methods and systems for diagnosing myocardial infarction in an emergency or cardiac unit, where cost is not a factor. What is important is accuracy of diagnosis and the system provides reflex algorithms which follow biomarker changes which are time sensitive in relation to the onset of myocardial infarct.

In contrast, the present invention addresses the problem of cost, efficiency and accuracy in clinical testing, often times in clinical laboratories and not in hospital wards. The present invention comprises of methods and systems which employ disease-specific algorithms, and provide cost effective, efficient, accurate and complete diagnostic information, and cut out the unnecessary tests. In fact, a test found to be negative is not repeated unless if it is suspected of experimental error.



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C. Armstrong et al. describes a method for diagnosis of acute myocardial infarction in which the biomarker measurement performed based on results from a precedent biochemical marker measurement step, is repeated at one of a plurality of different times subsequent to submission — col. 17, lines 14-18.

In contrast, the present invention provides an algorithmic clinical testing system using intelligent programming aimed at automated laboratory cost-cutting.

"It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention". *Hybritech Inc. v. Monoclonel Antibodies Inc.* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986). This is not the case in reference to Armstrong as described above.

Therefore, as a matter of law and fact, the rejection of claims 1-4 and 21-24 based on Armstrong et al. should be withdrawn.

2. Carson et al., U.S. Patent No. 6,140,065

The Action cites Carson et al. as disclosing computer assisted methods for differently diagnosing benign prostate disease and prostate adencarcinomas. The diagnostic method comprises five (5) steps of measuring total PSA, free PSA, factoring in age and applying the algorithm PV-$P_1$/(1-$P_1$). The free PSA measurements are done only if total PSA is between about 4.0 to 20.0 ng lmL.



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In response, applicant describes a prostate cancer algorithm, in which the total PSA of < 4.0 is negative, of 4 to 9.9 is equivocal (and requires measurement of free PSA) and > 10 is positive (and requires measurement of serum bone marker). Therefore, the prostate algorithm of the present invention is different in that levels of PSA greater than 10 trigger the measurement of serum bone marker. The prostate cancer algorithm of the present invention is an improved model over Carson et al's and thus can be distinguished from that of Carson et al. The rejection of claims 1-4 and 21-24 should be withdrawn.

3. Sreevatsan et al., J. Clin Micro. 1998, 36:1895-1901

The Action states that the present invention is anticipated by Sreevatsan et al., because the cited reference discloses reflex algorithms for the different diagnoses of Hepatitis C Virus stereotypes, and Figure 3 as setting forth the decision tree to be used in the process. Applicant disagrees with this rejection.

> "For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference - - - These elements must be arranged as in the claim under review, - - -." *In re Bond*, 910 F.2d 831, 15 USPQ 1566 (Fed. Cir. 1990)."

Sreevatsan et al. describes an algorithm approach to high-throughput molecular screening for alpha interferon-resistant genotypes for HCV detection. The study was designed to validate use of Cleavage Fragment Length Polymorphism

(CFLP) analysis as an alternative to DNA sequencing for high-throughput screening of HCV genotypes in a high-volume molecular pathology laboratory setting. (emphasis added Refer to Abstract). Thus, Sreevatsan et al. describe an algorithm that is suitable for use after the application of the algorithm for hepatitis of the present invention in a routine clinical laboratory. Clearly the elements for the Sreevatsan et al. algorithm for HCV genotypes and the elements for the hepatitis algorithm are different in all ways – in methodology, in decision making dependent on results of a preceding test, etc. Therefore, there is no basis as a matter of fact and law, pursuant to *In re Bond*, for the rejection of claims 1, 2 and 3 based on Sreevatsan. Applicant, respectfully requests that this rejection be withdrawn.

Applicant has made a diligent effort to place this application in condition for allowance and notice to the effect that claims 1-11 and 13-25 are in condition for allowance is earnestly solicited. If for any reason however, the Examiner should deem that this application is not in condition for allowance, the Examiner is respectfully requested to telephone the undersigned attorney at the number listed below to resolve any outstanding issues prior to issuing a further Office Action.

Respectfully submitted,

Rashida A. Karmali

Rashida A. Karmali, Esq.
Reg. No. 43,705
Attorney for Applicants
230 Park Avenue, Suite 1000
New York, New York 10169
Tel. No.: (212) 808-6589

Date: December 19, 2001

**CERTIFICATE OF FACSIMILE TRANSMISSION**

I hereby certify that this correspondence is being transmitted via Facsimile No 703-746-5279 to the attention of Mary Zeman at the United States Patent and Trademark Office, Washington, D.C. 20231 on December 19, 2001.

Rashida A. Karmall, Esq.
Attorney for Applicant

Rashida A. Karmali
Signature

12/19/01
Date of Signature

**<u>MARKED UP VERSION OF CLAIMS UNDER 37 C.F.R. 1.121(c)(1)(ii)</u>**

1.[A method of pipelining a disease-specific diagnostic algorithm on an n-bit data word stored in a memory said method comprising:

a) defining clinical tests used for the diagnosis of a disease

b) defining each of the clinical tests on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;

d) upon receiving a first of said clinical test value, computing the next clinical test

e) receiving a next one of said clinical tests of said data word;

f) computing a next portion of the diagnostic algorithm using said next of said clinical tests and a most recently calculated value of a computation of a prior portion of the diagnostic algorithm to produce a second clinical test value; and

g) if necessary, repeating steps (e) and (f) until all of said clinical tests of the data word have been processed, wherein the final value computed for the last clinical test is a value for the complete diagnosis of the specific disease.] <u>A method of pipelining a disease-specific diagnostic algorithm to achieve a cost-effective and accurate diagnosis, said method comprising the steps of:</u>



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a) classifying the various subgroups of the disease, said subgroups being classified based on pathology, pathogenic agent, cause or symptoms, on an n-bit data word stored in a memory;

b) defining the clinical tests suitable for confirming the diagnosis of each of the subgroups classified in a);

c) selecting to run the clinical tests listed in b) for the sub-group showing some abnormality and comparing the result with the normal value provided on the n-bit data word;

d) sequentially running the relevant clinical test of each of the sub-groups upon receiving a first of said clinical test values, and computing the next set of said clinical test for further testing, and

e) repeating steps c) and d) until a complete diagnosis of the specific disease type and group is provided, thereby avoiding unnecessary clinical tests and expensive duplicative procedures, while enabling an accurate diagnosis using the disease-specific diagnostic algorithm.



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2.The method of claim 1, further comprising performing a different clinical test after the value for the last clinical test is negative, to rule out a different diagnosis.

3.The method of claim 1, further comprising using a program code to implement the diagnostic algorithm.

4.The method of claim 3, further comprising using a modified computer architecture code to implement any modifications in the diagnostic algorithm.

5.The method of claim 1, [wherein the disease-specific diagnostic algorithm comprise the acid fast bacteria algorithm] The method according to claim 1, wherein said method is the acid fast bacteria algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of acid-fast bacteria;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values includes auramine smear and the next set of said clinical tests includes amplification; and



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e) receiving a next one of said clinical test of said data word, wherein the next of said clinical tests includes organism identification by DNA probe or biochemicals.

6.[The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the anemia algorithm] The method according to claim 1, wherein said method is the anemia algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of anemia, including myelodysplasia, leukemia, iron deficiency, or B-12/folate deficiency;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include WBC, MCV, ferritin, B12/folate and the next set of said clinical tests includes smear/image or reticulocyte count, hemoglobin ID, B-12 or folate respectively.

7. [The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the cardiac risk algorithm.] The method according to claim 1, wherein said method is the cardiac risk algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of cardiac risk, including abnormalities in cholesterol, triglycerides, LDL, HDL, homocysteine or anti-cardiolipn;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include cholesterol, HDL, triglycerides and the next set of said clinical tests includes homocysteines anticardio- lipin antibody, LDL by calculation or LDL by direct assay.

8.[The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the HbsAg algorithm.] The method of claim 1, wherein said method is the HbsAg algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of HbsAG;



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b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical test for further testing, wherein the first of said clinical test values include prenatal and dialysis specimen measurements of hepatitis B.

9. [The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the breast cancer algorithm.] The method according to claim 1, wherein said method is the breast cancer algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of breast cancer including genetic markers;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical test for further testing, wherein the first of said clinical test values include cancer marker 15-



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3, or cancer marker 27-29 and the next set of said clinical tests includes serum bone marker.

10.[The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the prostate cancer algorithm.] The method according to claim 1, wherein said method is the prostate cancer algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of prostate cancer including PSA for no risk, equivocal risk or positive cancer;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing wherein the first of said clinical test values include PSA (total) and the next set of said clinical tests includes free PSA or serum bone marker.

11. [The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the Epstein-Barr virus algorithm.] The method according to claim 1, wherein said method is the Epstein-Barr virus algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of Epstein-Barr virus, including viral capsid antigen, or Epstein Barr-Virus;



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b) defining each of th clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing wherein the first of said clinical test values include anti-EBV early antigen D, and the next set of said clinical tests includes anti VCA and EBNA.

12, [The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the Hepatitis algorithm.] Cancel.

13. [The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the thyroid function algorithm.] The method according to claim 1, wherein said method is the thyroid function algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of thyroid dysfunction;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;



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d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include TSH and the next set of said clinical tests includes FT-3 or FT-4.

14.[The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the autoimmune algorithm.] The method according to claim 1, wherein said method is the autoimmune algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of autoimmune disease including lupus;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include ANA and the next set of said clinical tests includes ds-DNA, HISTONE, Sm respectively, and

e) receiving a next one of said clinical test of said data word, wherein the next of said clinical tests includes SCL-70, RNP, SSA, SSB, SS-DNA.



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15. [The method of claim 1, wherein the disease-specific diagnostic algorithm comprises the serum protein algorithm.] The method according to claim 1, wherein said method is the serum protein algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of serum protein defect including serum protein electrophoresis;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include serum immuno fixation electrophoresis and the next set of said clinical tests includes quantitative assay of immuno globulin identified by SIFE.

16.[The method of claim 1, wherein the disease specific diagnostic algorithm comprises the urinalysis.] The method according to claim 1, wherein said method is the urinalysis algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis urine abnormalities;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;



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c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include protein, blood, leukocyte esterase omitrite and the next set of said clinical tests includes microscopic examination of urine.

17.[The method of claim 1, wherein the disease specific diagnostic algorithm comprises the human immunodeficiency virus.] The method according to claim 1, wherein said method is the human immunodeficiency algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of human immunodeficiency virus;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include HIV-1 and the next set of said clinical tests includes HIV-1 and HIV-2 respectively, and



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e) receiving a next one of said clinical test of said data word, wherein the next of said clinical tests includes HIV-2 WB

18.[The method of claim 1, wherein the disease specific diagnostic algorithm comprises the hepatitis B algorithm.] The method according to claim 1, wherein said method is the hepatitis B algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of hepatitis B, including HBsAg, HBsAb or SGPT;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include HBsAg(+), HBsAg(-)/HBsAb(+) or HBsAg(-)/HBsAb(-), and the next set of said clinical tests includes AFP/HBeAg/Ab, Immune or Hepatitis B(-) respectively,

e) receiving a next one of said clinical test of said data word, wherein the next of said clinical tests includes "Is HBe Ab present?".

f) . computing a next portion of the diagnostic algorithm using said next of said clinical tests and a most recently calculated value of a computation of a prior portion of the diagnostic algorithm to produce a second clinical test value; and

g) if necessary, repeating steps (e) and (f) until all of said clinical tests of the data word have been processed, wherein the final value computed for the last clinical test is a value for the complete diagnosis of hepatitis B.

19.[The method of claim 1, wherein the disease specific diagnostic algorithm comprises syphilis algorithm.] The method according to claim 1, wherein said method is the syphilis algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of syphilis;

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical test for further testing, wherein the first of said clinical test values include Elisa for T. Pallidum, and the next set of said clinical tests includes repeat Elisa and the rapid plasma regain test



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20.[The method of claim 1, wherein the disease specific diagnostic algorithm comprises the thrombophilia algorithm.] The method according to claim 1, wherein said method is the thrombophilia algorithm comprising the steps of:

a) defining the clinical tests used for the diagnosis of thrombophilia including LA/APA Alg(+) or APC-R(+);

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory;

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include LA-APA Alg(+) or APC-R(+) and the next set of said clinical tests includes homocysteine CRP; and

e) receiving a next one of said clinical test of said data word, wherein the next of said clinical tests includes Protein C, Protein S or AT-11.

21.An apparatus for pipelining a diagnostic algorithm on an n-bit data word, said apparatus comprising:

a. [a memory storing the n-bit data words;] a memory storing component, said component used for storing the n-bit data words relevant to a set of m clinical tests;

b. means for sequentially reading out each of a m clinical tests of the n-bit data from said memory, wherein m is an integer greater than one;

c. [m clinical tests, each of which is programmed to compute a different clinical test of the diagnostic algorithm using a different one of the m clinical tests to produce a corresponding result, wherein each of said clinical test after a first test receives the result from a prior stage and wherein the result from a prior stage and wherein the result from a last one of said m clinical tests is a complete diagnosis of a disease obtained by the no-bit data word.] <u>a processor for sequentially programming each of the m clinical tests to produce a complete diagnosis, and for outputting the result.</u>

22.The apparatus of claim 21, wherein the m clinical tests have an equal number of bits.

23.The apparatus of claim 21, wherein the memory comprises an array of chips, each of which includes a plurality of m-bit storage cells.

24.The apparatus of claim 23, wherein m equals at least one.

25.<u>The method according to claim 1, wherein said method is the lupus algorithm comprising the steps of:</u>

a) <u>defining the clinical tests for diagnosis of lupus anticoagulant/APA;</u>

b) defining each of the clinical tests listed in (a) on the n-bit data word and providing the normal value of each clinical test;

c) sequentially reading out each of said clinical test normal values of the n-bit data word from said memory; and

d) upon receiving a first of said clinical test values, computing the next set of said clinical tests for further testing, wherein the first of said clinical test values include DRVFT and the next set of said clinical tests includes LAC.



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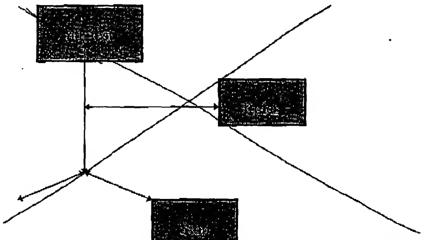
components in the test sample are washed away. Specifically-bound IgG reacts with a biotinylated anti-human IgG monoclonal antibody bound with streptavidin-horseradish peroxidase (HRP) during a second incubation period. Following a second wash cycle, specifically-bound enzyme conjugate is detected by reaction with hydrogen peroxide and the chromogen tetramethylbenzidine (TMB). The assay is measured spectrophotometrically to indicate the presence or absence of IgG treponemal antibodies.

4.14. Intelligent Programming Algorithm

The concept of the algorithm from a systems point of view is described in FIG. 18:



The result is compared by the computer with a rule which tells it whether and what test to order next in the sequence.

The nature of the rule depends on whether the nth assay generates a qualitative result (positive, negative or equivocal) or a quantitative (numerical) result. In the latter case actual results may be compared with the "reference range" for the healthy population.

This reference range can be developed in several different ways although CLS currently uses a curve fit routine (H. Martin et al, Normal Values in Clinical Chemistry (New York: Marcel Dekker, 1975). On the basis of the qualitative result or by comparison of the patient result with the reference range, the computer will stop or order the appropriate (n+l)st assay in the sequence.

In the present invention, the rules are applied through an expert system which is an intrinsic part of the architecture of the laboratory computer system. This expert system is an event-driven, expert rule based, decision-support software within the Cerner system.

*Rashida A. Karmali, Ph. D.*
ATTORNEY AT LAW
230 PARK AVENUE, SUITE 1000
NEW YORK, NEW YORK 10169

REGISTERED PATENT ATTORNEY
E-MAIL: karmali@aol.com

TEL: (212) 808-6589
FAX: (212) 808-6557

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**COMPANY:** Group 1631, PTO, US App Ser No 09/303,315
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**PHONE NO:**

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**FROM:** RASHIDA A. KARMALI
**No. of Pages:** 45
**Client:**

**MESSAGE:** Dear Examiner Zeman,
**I am attaching the AMENDMENT with the Petition for three months. I hope you will forgive me for the inconvenience I have caused you. Thanks for your patience.**

**Rashida A. Karmali**